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South Wales
NP10 8QQ

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The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference

PP/3395 GB

2. Patent application number
*(The Patent Office will fill in this part)*

9828853.3

30 DEC 1998

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Nycomed Amersham plc
Amersham Place
Little Chalfont
Buckinghamshire HP7 9NA
United Kingdom

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

7377419001

4. Title of the invention

NMR Spectroscopy Method

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

STEVENS HEWLETT & PERKINS
1 Serjeants' Inn
Fleet Street
LONDON
EC4Y 1LL

Patents ADP number *(if you know it)*

1545003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

*a) any applicant named in part 3 is not an inventor, or*
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Description 3

Claim(s) 1

Abstract

Drawing(s)

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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*

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11. I/We request the grant of a patent on the basis of this application.

Signature Stevens Hewlett & Perkins Date 30-12-98

Stevens, Hewlett & Perkins

12. Name and daytime telephone number of person to contact in the United Kingdom P Pennant; 0171-936-2499

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# NMR SPECTROSCOPY METHOD

This invention is concerned with nuclear magnetic resonance spectroscopy. The technique involves observing the spectrum of a nmr active nuclear species in order to obtain information about the environment in which the species is present. The spectra of nmr active nuclei vary depending on their environment, and this is reported in the literature (PNAS, 93,12932-6, 1996).

Noble gases having non-zero nuclear spin can be hyperpolarised, i.e. have their polarisation enhanced over the equilibrium polarisation, e.g. by the use of circularly polarised light. Preferred techniques for hyperpolarisation include spin exchange with an optically pumped alkali metal vapour and metastability exchange. Noble gases to which this technique can be applied include helium-3, neon-21, krypton-83, xenon-129 and xenon-131. As described by M S Albert *et al* in US Patent 5,545,396, the technique can be used to prepare hyperpolarised noble gases which can then be administered orally for magnetic resonance imaging of the human body.

Although chemically inert, xenon has hydrophobic properties, and is capable of being weakly bound by hydrophobic regions of biological molecules (PNAS, 78, No 8, 4946-9, August 1981; Abstracts of the 11$^{th}$ Annual Meeting of the Society for Magnetic Resonance in Medicine (1992) page 2104). Thus it is possible to "label" biological molecules with xenon. This invention arises from the idea of labelling biological molecules with hyperpolarised xenon-131 or more preferably xenon-129.

Thus in one aspect the invention provides a method which comprises labelling a biological molecule with hyperpolarised xenon, and observing a magnetic resonance spectrum of the hyperpolarised xenon in the environment of the biological molecule.

A biological molecule is a monomeric or polymeric molecule that is present in biological systems or that is artificially introduced and is biologically active in such systems. Biological molecules include lipids, sugars and polysaccharides, nucleic acids, drugs, and particularly peptides and proteins. Techniques for labelling such biological molecules with xenon are known in the art. Generally the biological molecule is present in a liquid medium into which the xenon is introduced either as a gas (e.g. by bubbling it through the fluid) or as a solution (e.g. in a lipid or fluorocarbon solvent). The xenon labels the biological compound by becoming weakly bound to it, e.g. at specific hydrophobic sites on a surface of a protein or other macromolecule.

In one aspect of the invention, the labelled biological molecule is subjected to nmr spectroscopy so as to examine the magnetic resonance spectrum of the hyperpolarised xenon. The spectrum provides information about the environment or environments at which atoms of xenon are bound to the biological molecule.

In another aspect, the invention provides an assay method which comprises using as an assay reagent a biological molecule labelled with hyperpolarised xenon. Labelling of the biological molecule with hyperpolarised xenon may be performed before, during or after performance of the assay. An assay is a test involving a reaction of one or more biological molecules, for example a competition assay, an immunoassay, a hybridisation assay or a binding assay, involving one or more lipids, saccharides, polynucleotides, peptides or proteins. Assays include binding studies performed on eukaryotic and prokaryotic microorganisms; binding studies performed on tissue *in vitro*; and binding studies in which an assay reagent is administered *in vivo* and an excretion product (e.g. urine, faeces, or breath) analysed by nmr spectroscopy.

By observing a change with time of an nmr spectrum, the progress can be followed of a reaction occurring during the course of an assay. Assays performed *ex vivo* may conveniently be in multiwell plates,

with either an assay reagent in the wells of the plate being labelled with hyperpolarised xenon, or a reagent being so labelled in bulk prior to being dispensed into individual wells of the plate.

Xenon-129 has a natural abundance of 26.4%. The xenon used for this invention may be either the naturally occurring material or one enriched in xenon-129. Bulk supplies of xenon enriched in xenon-129 and hyperpolarised to a high level are now available commercially and have a half life long enough to permit transport over substantial distances. While the half life of hyperpolarised xenon-129 in the biological environments contemplated in this invention will be lower, it is expected to be amply sufficient to permit the desired spectra to be obtained.

## CLAIMS

1. A method which comprises labelling a biological molecule with hyperpolarised xenon e.g. xenon-129, and observing a magnetic resonance spectrum of the hyperpolarised xenon in the environment of the biological molecule.

2. An assay method which comprises using as an assay reagent a biological molecule labelled with hyperpolarised xenon e.g. xenon-129.